tribute the observed variance in optical rotation to chemical rather than stereochemical considerations. Literature allegations[11] of the compound's stereochemical instability may stem in part from misinterpretation of previous literature[12] or experience with 1 obtained by other methods.[13]

The use of CH_2Cl_2 as solvent in the oxidation step dovetails well with the use of that same solvent in the purification process for the formation of diacetonide. Thus, the slurry can be the final process for diacetonide purification, and the material held as a solution, or the slurry can be incorporated as a pretreatment of diacetonide prior to the oxidation step. For large-scale work, diacetonide 2 has been treated in both fashions.

This chemistry has been scaled to 7500-L equipment, and multiple hundred-kilogram lots of aldehyde have been produced following essentially the procedure delineated previously with the same yield range observed on 5- and 10-g scale. It thus represents a highly reliable procedure for the synthesis of 2 in reasonable overall yield (34–36%).

Experimental Section[14]

1,2:5,6-Diisopropylidene-D-mannitol (2). To a vessel equipped with overhead agitator and reflux condenser was added D-mannitol (75 g, 0.41 mol), glyme (180 mL, freshly distilled), and 2,2-dimethoxypropane (120 mL, 0.98 mol). To this stirred mixture was added $SnCl_2$ (0.075 g, 0.4 mmol) and the mixture heated to reflux (ca. 74 °C) until a clear solution was obtained (ca. 1 h). The reaction was held at that temperature for 30 min then cooled to ambient temperature, and pyridine (0.09 mL, 1.14 mmol) was added. The solvents were removed in vacuo (6–10 mmHg, contents heated to 80–90 °C), and the residual material was cooled. The yield of 2 may be estimated by ^1H NMR (vs CH_2Cl_2, 32K data points, 6-s relaxation delay, 30° pulse) at this point. The crude material was slurried in CH_2Cl_2 (540 mL) at ambient temp for 1 h and then filtered to provide a solution containing 58 g of 2 (54%) as determined by capillary GC analysis (30 M DB-1, 145 °C vs internal standard dimethyl phthalate). A portion was removed, concentrated, and recrystallized (*n*-butyl ether): mp 121.8–123.4 °C (lit.[2a] mp 118–120 °C); $[\alpha]_D$ = +1.9° (*c* = 1.74, CH_3OH) (lit.[15] $[\alpha]_D$ = +1.9° (*c* = 2, CH_3OH)); ^1H NMR ($CDCl_3$) δ 4.22–4.10 (m, 4 H), 3.98 (dd, 2 H, *J* = 8.4, 5.4 Hz), 3.75 (approx. t, 2 H, *J* = 6.2 Hz), 2.70 (d, 2 H, *J* = 6.7 Hz), 1.42 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 109.39, 76.22, 71.16, 66.74, 26.72, 25.19; IR (KBr) 3400, 3292, 2980, 2933, 2895, 1386, 1372, 1265, 1212, 1070, 859 cm^{-1}. Anal. Calcd for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45. Found: C, 54.80; H, 8.50.

2,3-*O*-(Isopropylidene)-D-glyceraldehyde (1). Method A. To a vessel equipped with overhead agitator and thermometer was added diacetonide 2 (33 g, 0.13 mol) in CH_2Cl_2 (300–350 mL). Saturated aqueous $NaHCO_3$ (11.9 mL) was then added to the flask, maintaining the temperature at or below 25 °C. Solid $NaIO_4$ (52.8 g, 0.25 mol) was then added over a 20-min period with vigorous agitation and the reaction allowed to proceed for 2 h while the temperature was maintained below 30 °C. The solids were removed by filtration[16] and the filtrate was distilled at atmospheric pressure to a temperature of 55 °C. The residual oil was transferred to a smaller vessel and distilled at 30 mmHg; after a brief forerun, 22 g (67%) of 1 was obtained: bp 72–74 °C (30 mmHg); $[\alpha]_D$ = +80.1° (*c* = 1.534, benzene) (lit.[3j] $[\alpha]_D$ = +63.3° (*c* = 1.25, benzene); ^1H NMR ($CDCl_3$) δ 9.55 (d, 1 H, *J* = 1.8 Hz), 4.25 (m, 1 H), 4.05–3.93 (m, 2 H), 1.42 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 201.38, 110.79, 79.49, 65.11, 25.84, 24.73; IR (neat): 2990, 2940, 2890, 2820, 1730, 1375, 1250, 1215, 1150, 1070, 840 cm^{-1}; exact mass found 131.0710, calcd for $C_6H_{11}O_3$ $(M + H)^+$ 131.0708.

2,3-*O*-(Isopropylidene)-D-glyceraldehyde (1). Method B. To a vessel equipped with overhead agitator and thermometer was added diacetonide 2 (16.5 g, 60 mmol) in CH_2Cl_2 (150–175 mL) and saturated aqueous $NaHCO_3$ (6 mL). $NaIO_4$ (18.9 g, 84 mmol, 1.4 equiv) that had been sifted through a 140-mesh screen was then added in five portions over 20 min, with vigorous agitation, maintaining the temperature below 25 °C. After being stirred for 2 h, the solution was decanted into a second vessel, and the remaining solids were stirred with additional CH_2Cl_2 (53 mL) for 5 min.[16] This rinse was then combined with the CH_2Cl_2 solution and the solvent removed via atmospheric distillation (still-pot temperature <55 °C). The residual oil was then fractionally distilled (still-pot temperature <135 °C) through a Vigreux column. After a brief forerun at 67–72 °C, distillation provided 2 (12.0 g, 92 mmol, 72%) as an oil: bp 72–74 °C (30 mmHg); $[\alpha]_D$ = +73.1° (*c* = 1.34, benzene). Spectral data as in the previous text. Exact mass found 131.0709, calculated for $C_6H_{11}O_3$ $(M + H)^+$ 131.0708.

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Registry No. 1, 15186-48-8; 2, 1707-77-3; D-mannitol, 69-65-8.

Supplementary Material Available: ^1H NMR spectra for compound 2 prepared by both methods (2 pages). Ordering information is given on any current masthead page.

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(13) While this manuscript was being readied for release, we became aware of independent work within Lilly that confirmed these findings. See: Hertel, L. W.; Grossman, C. S.; Kroin, J. S. *Synth. Commun.* **1991**, *21*, in press.

(14) Melting and boiling points are uncorrected. Proton and carbon NMR spectra were obtained at 300 and 75.5 MHz, respectively, and are referenced to residual protonated solvent or internal TMS. HRMS and combustion analyses were performed by Molecular Structure Research at Eli Lilly and Co.

(15) *Aldrich Catalog Handbook of Fine Chemicals, 1990–1991*; Aldrich Chemical Co., Inc.: Milwaukee, WI, 1990; p 487.

(16) The mixed oxidation state iodate/periodate salts recovered from this procedure show instability that increases with scale. We recommend timely decomposition of the salts in aqueous solution using either sodium thiosulfate or sodium bisulfite for reaction scales larger than 1 mol.

(17) **Note Added in Proof:** More recently, repetition of the Jackson procedure afforded an 84% yield, more consistent with the author's findings, when the $MgSO_4/NaIO_4$ filter cake rinse was performed by careful reslurry in dichloromethane followed by filtration. Thus, while the present optimized procedure avoids the use of large excesses (200 mol % relative to 2) of $MgSO_4$ dessicant and is therefore better suited to large scale, small-scale needs may be better served by including the drying protocol.

Preparation of Noncondensed 2-Substituted 1-Methylimidazoles via Ipso Substitution Reaction on 2-Sulfinyl or 2-Sulfonyl Derivatives of 4,5-Disubstituted 1-Methylimidazoles

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Introduction

Heteroaromatic nucleophilic addition–elimination reactions are commonly recognized in many electron-deficient heterocycles. However, literature reports of this reaction with electron-rich imidazoles and condensed imidazoles are uncommon, with few examples of the former.[1] During the course of our continuing research in the de-

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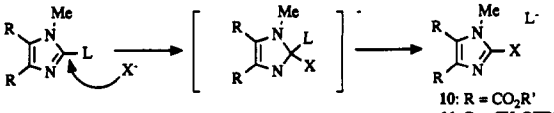
0022-3263/91/1956-4058$02.50/0

Table I. Results of Ipso Substitution Reactions on Imidazoles 2, 3, 8, and 9



10: R = CO_2R'
11: R = $CH_2OTBDMS$
12: R = CH_2OCH_2Ph

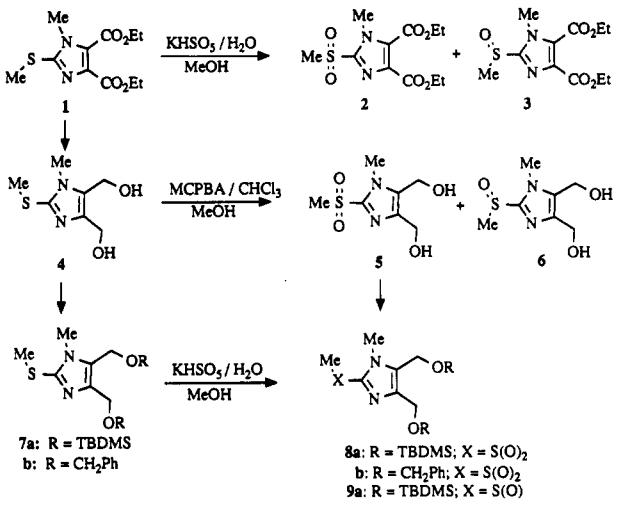
substrate (L/R)	nucleophile (X^-)	solvent	reaction time, (temp, °C)	% yield[a] (product)
2 [$MeS(O)_2/CO_2Et$]	MeO^-	MeOH	5 (45)	91 (**10a**)
	EtO^-	EtOH	1 (67)	77 (**10b**)
	n-PrO^-	*n*-PrOH	1 (81)	73 (**10c**)
	PhS^-	THF	21 (50)	82 (**10d**)
	N_3^-	DMF	13 (87)	42 (**10e**)
	N_3^-	DMF	11 (23)	NR
	N_3^-	DMF-MeOH	27 (87)	see text
3 [$MeS(O)/CO_2Et$]	MeO^-	MeOH	1 (65)	73 (**10a**)
	EtO^-	EtOH	1 (61)	62 (**10b**)
	N_3^-	DMF	74 (87)	14 (**10e**)
8a [$MeS(O)_2/CH_2OTBDMS$]	MeO^-	MeOH	27 (65)	98[b] (**5**)
	PhS^-	THF	27 (71)	81 (**11d**)
	N_3^-	DMF	4 (87)	NR
	$PhCH_2NH_2$	EtOH	8 (65)	NR
	n-$PrNH_2$	neat	12 (41)	NR
	n-$PrNH_2$	25% EtOH	12 (67)	NR
9a [$MeS(O)/CH_2OTBDMS$]	MeO^-	MeOH	27 (65)	89[b] (**6**)
	PhS^-	THF	24 (71)	72 (**11d**)
8b [$MeS(O)_2/CH_2OCH_2Ph$]	MeO^-	MeOH	21 (65)	87 (**12a**)
	PhS^-	THF	27 (71)	69 (**12d**)
	N_3^-	DMF	14 (81)	NR
	n-$PrNH_2$	25% EtOH	71 (47)	NR

[a] Yields were based on loss of starting material when azide was used. [b] Yields represent recovery of deprotected diol, no substitution occurred.

velopment of bifunctional alkylating agents as drugs for the treatment of neoplastic disease,[2] we required a new method for the preparation of highly functionalized, noncondensed imidazoles. We now report the first examples of the utility of 2-(methylsulfinyl)- and 2-(methylsulfonyl)imidazoles as substrates for ipso substitution reactions using anionic nucleophiles (alkoxide, azide, thiolate) to provide the corresponding 2-substituted imidazole in moderate to high yields. Particularly important to this paper are the state of activation of the heterocyclic substrate and the effect of the leaving group on reactivity. Shepherd and Fedrick have reported the reactivity of electron deficient azines with simple nucleophiles,[3] but the considerable industrial and medicinal importance of imidazole derivatives and the widespread interest in their chemistry makes the extension of ipso substitution on noncondensed imidazoles an important addition to this methodology.

The plan for ipso substitution reactions on the noncondensed imidazole substrates **2**, **3**, **8**, and **9** derived from two considerations. First, alkyl- or arylsulfinyl or -sulfonyl substituents as leaving groups in electron-deficient heteroaromatic systems have been reported to have reactivity equivalent to, or greater than, that of a chloro group.[4] Second, activation by electron-withdrawing 4,5-dicarboxylate substituents in conjunction with the C-2 substituent may lower the transition state energy enough to allow the ipso substitution to occur. There are no literature reports on the use of sulfinyl or sulfonyl substituents as leaving groups on imidazoles and there is only one example[5] where a 2-sulfonylbenzimidazole derivative was

Scheme I



7a: R = TBDMS
b: R = CH_2Ph

8a: R = TBDMS; X = $S(O)_2$
b: R = CH_2Ph; X = $S(O)_2$
9a: R = TBDMS; X = S(O)

hydrolyzed to the benzimidazol-2-one under strongly alkaline conditions. However, considering the degree of reactivity of the sulfonyl group and the ease of synthesis, further exploitation of this substrate type may have widespread synthetic utility.

Results and Discussion

Diethyl 1-methyl-2-(methylthio)imidazole-4,5-dicarboxylate (**1**)[2] was oxidized[6] using excess Oxone (49.5% potassium hydrogen persulfate) to give a mixture of sulfone **2** and sulfoxide **3** in a 4:1 ratio. Reduction of **1** with lithium aluminum hydride gave the bis(hydroxymethyl) derivative **4**. Oxidation of the thioether **4** to the sulfone and sulfoxide

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could be done either prior to or after protection of the hydroxymethyl substituents. Both methods furnished 8 and 9; however, the latter method was more efficient in that the sulfones and sulfoxides were more easily isolated than the more polar (water soluble) diols 5 and 6. Therefore, diol 4 was protected either as the bis(*tert*-butyldimethylsilyl) ether **7a** (*tert*-butyldimethylsilyl chloride, triethylamine, and catalytic (dimethylamino)pyridine) or as the dibenzyl ether **7b** (sodium hydride–benzyl bromide).

Our studies on the reactivity of various 2-(methylsulfinyl)- and 2-(methylsulfonyl)imidazole derivatives toward anionic nucleophiles are shown in Table I. The degree of ring activation was modulated by the oxidation state of the 4- and 5-substituents. The imidazole-4,5-dicarboxylates 2 and 3 are more activated toward nucleophilic attack and can better stabilize the increase in electron density due to the incoming nucleophile than the reduced 4,5-bis(hydroxymethyl)imidazole derivatives 8 and 9. This is due to the change in electron-withdrawing character of these substituents. The transition state and the intermediate complex[3] are better stabilized when the disruption of the aromatic π system can be partially offset by delocalizing electron density onto the substituents at the 4- and 5-positions.

The sulfones and sulfoxides were treated with the various nucleophiles listed in Table I. In the cases where alkoxide was used as the nucleophile, ipso substitution occurred rapidly and in high yield. Transesterification was expected when 2 and 3 were substrates, so a 5-fold excess of attacking alkoxide was used. Alcoholic HCl was used to quench the reaction mixture to avoid aqueous hydrolysis of the 2-alkoxyimidazole product in a manner similar to that reported[7] for 2-methoxy-1-methylbenzimidazole. When methoxide was reacted with **8a** and **9a** the unexpected cleavage of the silyl protecting groups led to the isolation of 5 and 6 in near quantitative yield. The cleavage products were characterized by comparison (TLC and ^{1}H NMR) to 5 and 6 prepared independently by peracid oxidation. The imidazole substrate carrying benzyl ether protecting groups **8b** allowed unhindered displacement by methoxide.

The thiophenolate anion was used as a nucleophile to give **10d** from 2; the less reactive imidazoles, 8 and 9, afforded **11d** and **12d** in good yield. No sulfur reduction was detected in reactions with the 2-(methylsulfinyl)-imidazoles, 3 and **9a**, as has been reported[8] for reactions of (methylsulfinyl)pyridines with similar anionic nucleophiles.

Azide displacement of both the methylsulfonyl and methylsulfinyl substituents occurred (in lower yields) with 2 and 3 but failed with the less activated substrates 8 and 9 under a variety of conditions. The use of a protic solvent, anhydrous DMF–methanol (1:1), led to longer reaction times for the azide displacement, lower yields (ca. 4%), and a mixture of partially and completely transesterified products. Attempts were made to displace both sulfone and sulfoxide in the less active bis(hydroxymethyl)-protected substrates 8 and 9 with nonionic nucleophiles (propylamine and benzylamine) but only starting material was recovered.

The results show that imidazole substrates 2 and 3 are more reactive toward ipso substitution than 8 and 9. The data also show that displacement reactions with the sulfone moiety gave higher yields than with the corresponding sulfoxide under similar reaction conditions. The latter observation can be attributed to both the increased activation of the methylsulfonyl group toward nucleophilic attack and to the stability of the departing leaving group. These sulfur leaving groups have the potential to find more general use in other systems, where further ring activation could be achieved through the placement of electron-withdrawing substituents at the remaining positions in the imidazole ring.

Experimental Section

Melting points (uncorrected) were determined in an open capillary. IR spectra were determined with a FT-IR interferometer. ^{1}H NMR spectra were determined at 90 MHz. Microanalyses were performed by Atlantic Microlab, Atlanta, GA. Silica gel for flash column chromatography (230–400 mesh ASTM) was obtained from EM Science.

Diethyl 1-Methyl-2-(methylsulfonyl)imidazole-4,5-dicarboxylate (2) and Diethyl 1-Methyl-2-(methylsulfinyl)-imidazole-4,5-dicarboxylate (3). A solution of Oxone (Alpha Products, 49.5% potassium hydrogen persulfate, 60.1 g, 3 equiv, 250 mmol) in water (200 mL) was added, with stirring, over 15 min to a solution of crude diethyl 1-methyl-2-(methylthio)-imidazole-4,5-dicarboxylate[2] (1, 22.04 g, 82.7 mmol) in methanol (200 mL) at 2 °C. A yellow–white suspension developed immediately. The mixture was stirred at room temperature for 4 h and then concentrated in vacuo to ca. 200 mL to remove the methanol. Water (100 mL) was added, the mixture was extracted with dichloromethane (3 × 120 mL), and the combined organic phase was washed with brine (2 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography of the white residue afforded 2 (eluted with hexane–EtOAc, 1:2) as a white solid (15.86 g, 63%) and 3 (eluted with EtOAc) as a yellow oil (3.52 g, 15%). The sulfone 2 had the following properties: mp 79.5–80.5 °C; ^{1}H NMR δ 1.30 (t, 3 H), 1.32 (t, 3 H), 3.47 (s, 3 H), 4.10 (s, 3 H), 4.35 (q, 2 H), 4.42 (q, 2 H); IR (KBr) 2994, 2918, 1718 s, 1476, 1329 s, 1225 s, 1167, 786 cm^{-1}. Anal. Calcd for $C_{11}H_{16}N_2O_6S$: C, 40.50; H, 5.30; N, 9.20; S, 10.56. Found: C, 40.50; H, 5.32; N, 9.16; S, 10.48.

The sulfoxide 3 had the following properties: ^{1}H NMR (MeOH-d_4) δ 1.33 (t, 3 H), 1.38 (t, 3 H), 3.19 (s, 3 H), 4.05 (s, 3 H), 4.36 (q, 2 H), 4.39 (q, 2 H); IR (neat) 3449, 2983, 1724 s, 1468, 1205 s, 1043 cm^{-1}. Anal. Calcd for $C_{11}H_{16}N_2O_5S$: C, 45.83; H, 5.59; N, 9.71; S, 11.12. Found: C, 45.72; H, 5.60; N, 9.70; S, 11.14.

4,5-Bis(hydroxymethyl)-1-methyl-2-(methylsulfonyl)-imidazole (5) and 4,5-Bis(hydroxymethyl)-1-methyl-2-(methylsulfinyl)imidazole (6). *m*-Chloroperbenzoic acid (1.9 equiv, 12.33 mmol) was added portionwise at −5 °C (under argon) to a stirred solution of diol[2] 4 (1.25 g, 6.64 mmol) in anhydrous dichloromethane–methanol (1:1, 30 mL). The mixture was kept at −5 °C for 3 h then brought to 18 °C over 11 h. The clear solution was concentrated to dryness in vacuo, and the residue was dissolved in dichloromethane–methanol (3:1, 10 mL) and purified by flash column chromatography (methanol–dichloromethane, 1:9) to give sulfone 5 as a yellow solid (800 mg, 55%). The minor product was the sulfoxide 6 as a clear oil (400 mg, 30%) which solidified upon standing. 5: mp 139–140 °C; ^{1}H NMR (methanol-d_4) δ 3.32 (s, 3 H), 3.97 (s, 3 H), 4.31 (s, 2 H), 4.50 (s, 2 H), 4.71 (s, 2 H); IR (KBr) 3395, 3201 br, 3001, 2920, 1477 s, 1414, 1366, 1323, 1149, 1115, 1031 s, 961 cm^{-1}. Anal. Calcd for $C_7H_{12}N_2O_4S$: C, 38.17; H, 5.49; N, 12.72; S, 14.56. Found: C, 38.20; H, 5.53; N, 12.62; S, 14.46.

Sulfoxide 6: mp 105–107 °C; ^{1}H NMR (acetone-d_6) δ 3.12 (s, 3 H), 3.94 (s, 3 H), 4.58 (s, 2 H), 4.69 (s, 2 H), 4.80 (s, 2 H); IR (neat) 3408–3305 br, 1469, 1406, 1013 s cm^{-1}. Anal. Calcd for $C_7H_{12}N_2O_3S$·0.5H_2O: C, 39.43; H, 6.15; N, 13.14; S, 15.04. Found: C, 39.68; H, 6.09; N, 13.04; S, 14.89.

4,5-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1-methyl-2-(methylthio)imidazole (7a). A stirred suspension of diol[2] 4 (250 mg, 1.33 mmol) in anhydrous dichloromethane (15 mL) at 2 °C (under argon) was treated sequentially with triethylamine (2.4 equiv, 0.40 mL), *tert*-butyldimethylsilyl chloride (2.2 equiv, 2.92 mmol, 0.440 g), and 4-(dimethylamino)pyridine (0.1 equiv). The stirred mixture was kept at 2 °C for 15 min and then brought

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(8) Furuhawa, N.; Ogawa, S.; Kawai, T. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1839.

to room temperature and stirred for 20 h. The white suspension was concentrated in vacuo, and the tan residue was dissolved in methanol (3 mL) and purified by flash chromatography (hexane–EtOAc, 5:1) to give **7a** as a colorless oil (460 mg, 83%): ^{1}H NMR δ 0.02 (s, 6 H), 0.05 (s, 6 H), 0.86 (m, 18 H), 2.46 (s, 3 H), 3.50 (s, 3 H), 4.60 (s, 2 H), 4.68 (s, 2 H); IR (neat) 2952, 2928, 2856, 1461, 1253, 1056, 837 cm^{-1}. Anal. Calcd for $C_{19}H_{40}N_2O_2SSi_2$: C, 54.76; H, 9.67; N, 6.72; S, 7.69. Found: C, 54.62; H, 9.70; N, 6.67; S, 7.63.

4,5-Bis[(benzyloxy)methyl]-1-methyl-2-(methylthio)-imidazole (7b). Diol[2] **4** (3.0 g, 15.94 mmol) was added to a stirred suspension of sodium hydride (2.2 equiv, 35.1 mmol, 842 mg) in anhydrous THF (50 mL) at 2 °C (argon). The suspension was stirred for 20 min, benzyl bromide (2.5 equiv) was added by syringe, and the mixture was stirred at ambient temperature for 6 h. The excess hydride was destroyed with methanol at 2 °C, and the mixture was concentrated in vacuo. The orange, oily residue was partitioned between ether–water (1:1, 125 mL), and the organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo to an orange oil. The residue was purified by flash chromatography (hexane–EtOAc, 1:1) to give **7b** as a clear yellow oil (4.52 g, 77%): ^{1}H NMR δ 2.57 (s, 3 H), 3.50 (s, 3 H), 4.37–4.63 (m, 8 H), 7.28 (m, 10 H); IR ($CDCl_3$) 3042, 2933, 2855, 1454, 1064 s, 923 cm^{-1}. Anal. Calcd for $C_{21}H_{24}N_2O_2S$: C, 68.45: H, 6.56; N, 7.60; S, 8.70. Found: C, 68.35; H, 6.58; N, 7.53; S, 8.63.

4,5-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1-methyl-2-(methylsulfonyl)imidazole (8a) and 4,5-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1-methyl-2-(methylsulfinyl)-imidazole (9a). Sodium acetate (10 equiv, 24.0 mmol, 3.27 g) was added to a solution of **6a** (1.0 g, 2.4 mmol) in methanol (10 mL), and the mixture was treated with a solution of Oxone (49.5% potassium hydrogen persulfate, 3.0 equiv, 1.75 g) in water (10 mL) at room temperature with stirring. The white suspension was stirred for 15 h and suction filtered, and the solid was washed with methanol (3 × 10 mL). The combined filtrate was concentrated in vacuo to give an off white residue. The residue was partitioned between dichloromethane (15 mL) and water (15 mL), and then the aqueous phase was washed with dichloromethane (2 × 20 mL). The combined organic solution was dried ($MgSO_4$) and concentrated in vacuo to a clear oil that was purified by flash chromatography (5% methanol in dichloromethane) to give sulfone **8a** (the major product, R_f = 0.62) as clear oil (540 mg, 52%) which solidified upon standing. The minor product was the sulfoxide **7a** (R_f = 0.32). The sulfone **8a** had the following properties: mp 59–60 °C; ^{1}H NMR ($CDCl_3$) δ 0.1 (s, 12 H), 0.9 (s, 18 H), 3.38 (s, 3 H), 3.98 (s, 3 H), 4.68 (s, 2 H), 4.80 (s, 2 H); IR (neat) 2955, 2929, 2857, 1471, 1312, 1257, 1144, 1103, 1021 s, 838 s cm^{-1}. Anal. Calcd for $C_{19}H_{40}N_2O_4Si_2S$: C, 50.80; H, 8.98; N, 6.24. Found: C, 50.65; H, 8.92; N, 6.21.

The sulfoxide **9a** had the following properties: ^{1}H NMR ($CDCl_3$) δ 0.1 (s, 12 H), 0.9 (s, 18 H), 3.19 (s, 3 H), 3.91 (s, 3 H), 4.68 (s, 2 H), 4.78 (s, 2 H); IR (neat) 2986, 2931, 2848, 1462, 1247, 1060 s, 838 cm^{-1}. Anal. Calcd for $C_{19}H_{40}N_2O_3Si_2S$: C, 52.76; H, 9.32; N, 6.47. Found: C, 52.43; H, 9.26; N, 6.54.

4,5-Bis[(benzyloxy)methyl]-1-methyl-2-(methylsulfonyl)imidazole (8b). A solution of **7b** (2.16 g, 5.86 mmol) in methanol (20 mL) was treated with a solution of Oxone (3 equiv) in water (20 mL) in the same manner as **7a** except the Oxone was added at 25 °C and the reaction time was 18 h. The reaction mixture was extracted with chloroform (3 × 40 mL). Flash chromatography (5% methanol in dichloromethane) afforded **8b** as a clear yellow oil (2.24 g, 95%): ^{1}H NMR δ 3.31 (s, 3 H), 3.87 (s, 3 H), 4.46 (s, 4 H), 4.53 (s, 4 H), 7.28 (m, 5 H); IR (neat) 3029, 2925, 2861, 1471, 1454, 1310 s, 1145, 1112, 1068, 1027 cm^{-1}. Anal. Calcd for $C_{21}H_{24}N_2O_4S$: C, 62.98; H, 6.04; N, 6.99; S, 8.01. Found: C, 62.88; H, 6.08; N, 6.91; S, 7.99.

General Procedure for the Preparation of 2-Alkoxyimidazoles.[9] Dimethyl 2-Methoxy-1-methylimidazole-4,5-dicarboxylate (10a). Sodium metal (5 equiv, 0.76 g, 32.86 mmol) was dissolved in absolute methanol (25 mL) at room temperature under strict anhydrous conditions, and then a solution of the sulfone **3** (2.09 g, 6.57 mmol) in anhydrous THF (7 mL) was added dropwise to give an immediate white suspension. The reaction mixture was gently heated at 45 °C for 5 h with stirring. TLC (hexane–EtOAc, 1:1) showed complete disappearance of starting material after 2.5 h. The yellow solution was cooled to 20 °C and quenched with dry methanolic HCl (8 mL) to adjust the pH to 8 (litmus paper), and the resultant suspension was filtered. Silica gel (5 g) was added to the filtrate, the mixture was concentrated in vacuo, and the free-following solid residue was loaded onto a wet flash column (hexane–EtOAc, 2:3). Compound **10a** was obtained as a clear oil that solidified to a white solid upon standing (1.29 g, 91%): mp 62–63 °C (lit.[3] mp 62–63 °C); ^{1}H NMR δ 3.56 (s, 3 H), 3.87 (s, 6 H), 4.14 (s, 3 H); IR ($CDCl_3$) 2951, 1709 s, 1732 s, 1559, 1338, 1282, 1206 s, 1116 cm^{-1}.

Diethyl 2-Ethoxy-1-methylimidazole-4,5-dicarboxylate (10b). The procedure used for the preparation of **10a** was modified to use sodium ethoxide solution in absolute ethanol (and absolute ethanol–HCl in the workup) to give **10b** (77%): mp 38–39 °C; ^{1}H NMR δ 1.21–1.57 (m, 9 H), 3.58 (s, 3 H), 4.18–4.55 (m, 4 H), 4.56 (q, 2 H); IR (neat) 2982, 1710, 1552, 1193, 1045, cm^{-1}. Anal. Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.71; N, 10.36. Found: C, 53.42; H, 6.73; N, 10.34.

Dipropyl 1-Methyl-2-propoxyimidazole-4,5-dicarboxylate (10c). The procedure used for the preparation of **10a** was modified to use sodium propoxide in anhydrous propanol (and anhydrous propanol–HCl in the workup) to give **10c** (73%) as a clear oil: ^{1}H NMR δ 0.87–1.18 (m, 9 H), 1.61–2.04 (m, 6 H), 3.58 (s, 3 H), 4.14–4.43 (m, 4 H), 4.40 (q, 2 H); IR ($CDCl_3$) 2970, 2939, 2881, 1709, 1552, 1498, 1469, 1362, 1342, 1275, 1196, 1112, 1040, 981 cm^{-1}. Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.68; H, 7.74; N, 8.96. Found: C, 57.61; H, 7.76; N, 8.88.

Diethyl 1-Methyl-2-(phenylthio)imidazole-4,5-dicarboxylate (10d). Sodium hydride (5 equiv, 8.2 mmol) was added to a solution of thiophenol (7 equiv, 11.48 mmol) in anhydrous THF (10 mL) at 40 °C, and then a solution of the sulfone **2** (0.5 g, 1.64 mmol) in anhydrous THF (3 mL) was added in one aliquot (syringe) and the white suspension was stirred at 50 °C for 21 h. Ethanolic HCl (ca. 5 mL) was added until pH 8 on litmus, and the yellow suspension was dissolved in water (30 mL) and extracted with chloroform (3 × 30 mL). The combined organic solution was washed with saturated aqueous sodium bicarbonate (3 × 40 mL), dried ($MgSO_4$), and concentrated in vacuo. The clear oily residue was purified by flash chromatography (hexanes–EtOAc, 3:1) to give **10d** as a clear oil (450 mg, 82%): ^{1}H NMR δ 1.38 (t, 6 H), 3.78 (s, 3 H), 4.43 (q, 4 H), 7.28 (s, 5 H); IR (neat) 2782, 1719 s, 1458, 1271, 1203 s cm^{-1}. Anal. Calcd for $C_{16}H_{18}N_2O_4S$: C, 57.47; H, 5.43; N, 8.32; S, 10.77. Found: C, 57.34; H, 5.44; N, 8.34; S, 10.64.

Diethyl 2-Azido-1-methylimidazole-4,5-dicarboxylate (10e). A stirred solution of sulfone **2** (2.0 g, 6.57 mmol) in anhydrous DMF (10 mL) was treated with sodium azide (3 equiv, 1.28 g, 19.71 mmol) at room temperature (argon). The mixture was heated at 87 °C for 13 h, cooled to 25 °C, and poured into water (20 mL). The aqueous mixture was extracted with chloroform (3 × 25 mL), and the organic phase was washed with water (2 × 25 mL) and brine (2 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo to a yellow oil. Flash chromatography (hexane–EtOAc, 2:1) of the resultant oil gave recovered starting material (1.30 g, 4.27 mmol) and **10e** as a clear yellow oil (230 mg, 42%, based on unrecovered starting material): ^{1}H NMR δ 1.35 (t, 3 H), 1.38 (t, 3 H), 3.58 (s, 3 H), 4.43 (q, 2 H), 4.63 (q, 2 H); IR ($CDCl_3$) 2986, 2169 s, 2144 s, 1710 s, 1503, 1495, 1379, 1275, 1202 s cm^{-1}. Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.95; H, 4.90; N, 26.20. Found: C, 45.01; H, 4.94; N, 26.14.

4,5-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1-methyl-2-(phenylthio)imidazole (11d). Compound **11d**, prepared either from **8a** or **9a** (see Table I) by using the method described for the preparation of **10d**, was purified by flash chromatography (hexane–EtOAc, 9:1) and was obtained as a clear oil: ^{1}H NMR δ 0.05 (s, 6 H), 0.09 (s, 6 H), 0.85 (s, 9 H), 0.91 (s, 9 H), 3.62 (s, 3 H), 4.75 (s, 2 H), 4.80 (s, 2 H), 7.18 (s, 5 H); IR ($CDCl_3$) 2954, 2930, 2857, 1471, 1482, 1455, 1258, 1067, 898, 838 cm^{-1}. Anal. Calcd for $C_{24}H_{42}N_2O_2Si_2S$: C, 60.20; H, 8.84; N, 5.85; S, 6.70. Found: C, 60.17; H, 8.89; N, 5.85; S, 6.60.

4,5-Bis[(benzyloxy)methyl]-2-methoxy-1-methylimidazole (12a). The procedure used to make **10a** was used with sulfone

(9) Addition of imidazole substrate was usually at increased temperature and as a solid. The reactions were quenched with HCl gas in the corresponding alcohol. The same conditions were used for the sulfoxide substrates.

8b. After a 24-h reaction time, the reaction mixture was concentrated to half volume, poured onto water (20 mL), extracted with ether (3 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo to give **12a** as a yellow oil (87%): ^1H NMR (MeOH-d_4) δ 3.30 (s, 3 H), 3.97 (s, 3 H), 4.35 (s, 2 H), 4.39 (s, 2 H), 4.43 (s, 2 H), 4.50 (s, 2 H), 7.27 (s, 10 H); IR (neat) 3029, 2940, 2857, 1553, 1507, 1064, 1027 cm^{-1}. Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.84; H, 6.76; N, 7.89.

4,5-Bis[(benzyloxy)methyl]-1-methyl-2-(phenylthio)-imidazole (12d). The procedure used to make **10** was used with sulfone **8b** (except that the reaction mixture was not acidified before workup) to give **12a** as a clear yellow oil (3.72 g, 69%): ^1H NMR (acetone-d_6) δ 3.64 (s, 3 H), 4.48 (s, 2 H), 4.53 (s, 2 H), 4.58 (s, 2 H), 4.65 (s, 2 H), 7.28 (m, 15 H); IR (neat) 3077, 3028, 1441, 1358, 1067 s, 1028 s cm^{-1}. Anal. Calcd for $C_{26}H_{26}N_2O_2S \cdot 0.25H_2O$: C, 71.78; H, 6.14; N, 6.44; S, 7.37. Found: C, 71.78; H, 6.14; N, 6.43; S, 7.27.

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Ab Initio Calculations on the Diazirinyl Anion. A Nonaromatic Species

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In 1965 Breslow proposed the term antiaromatic to describe compounds which are destabilized by cyclic conjugation.[1] This idea was extremely appealing because many 4π-electron systems were known to be difficult to prepare and quite reactive. Subsequent work on cyclopropenyl anion, cyclobutadiene, and cyclopentadienyl cation has led to a general consensus that these small antiaromatic systems are indeed destabilized by conjugation.[2] This point of view, however, has been questioned,[3] and given the continuing interest in this area, along with the recent gas-phase formation of the diazirinyl anion (**1a**),[4] we decided to investigate this novel species via molecular orbital calculations.

Ab initio calculations using the Gaussian series of programs[5] have been carried out on diazirine (**1**), four of its isomers, the corresponding conjugate bases, and several related compounds. Full geometry optimizations at the Hartree-Fock level were carried out with the 6-31+G* basis set.[6] All of the structures were characterized by their vibrational frequencies to insure that they correspond to local minima (no imaginary frequencies) or transition states (one imaginary frequency) on the potential energy surface. Polarization functions and diffuse orbitals, which are required to adequately describe molecules with heteroatoms, stained rings, and a negative charge, are included in this basis set.[7] Electron correlation was accounted for in the energy calculations with second-order Møller-Plesset theory (MP2),[8,9] and the resulting deprotonation energies (DPEs) were corrected for zero-point vibrational energies (calculated at HF/6-31+G*). The results are summarized in Table I and are in reasonable accord with experiment. It is interesting to note that the errors for the hydrocarbons are on the order of 1-2 kcal mol^{-1}, in agreement with previous results,[10] whereas they are somewhat larger for

Table I. Calculated and Experimental Acidities

compound[a]	acidity[b] 6-31+G*[c]	MP2[d]	AM1	expt
$CH_2{=}N{=}N$	392.6 (384.7)	375.0 (367.1)	384.9	373 ± 3[e]
NH_2CN	360.2 (351.8)	351.9 (343.5)	361.6	350 ± 3[f]
NH_2NC	372.7 (363.9)	357.8 (349.0)	361.7	-
 1	414.2 (404.9)	405.2 (395.9)	389.9	401 ± 3[f]
→  2	364.8 (356.6)	362.3 (354.1)	362.4	-
→  3	cis[g] 415.5 (406.5)	406.4 (397.4)	391.4	-
	trans 421.2 (411.8)	412.2 (402.8)	395.3	-
→ $CH_3CH{=}CH_2$	408.0 (398.1)	398.6 (388.7)	386.7	390.8 ● 2[e]
→  4	438.5 (428.7)	428.4 (418.6)	423.2	-
 5	431.8 (422.2)	422.5 (412.8)	415.5	412 ± 3[h]

[a] When more than one acidic site is present the arrow indicates the position for which the acidity has been calculated. [b] All values in kcal mol^{-1}. [c] Geometries, energies, and frequencies were calculated at the 6-31+G*//6-31+G* level of theory. The numbers in parentheses have been corrected for zero point energy (zpe) differences using scaled frequencies (0.90). [d] MP2/6-31+G*//6-31+G* energies. The numbers in parentheses are acidities corrected for the z.p.e as explained in note *c*. [e] Reference 20. [f] Reference 4. [g] The two methylene hydrogens are distinct in the cis compound. The acidity reported here corresponds to the removal of the proton which is cis to the hydrogens on nitrogen. [h] The uncertainty is estimated.

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